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bjh research paper

Increased risk of arterial thromboembolism after a prior episode of venous thromboembolism: results from the Prevention of REnal and Vascular ENd stage Disease (PREVEND) Study

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Summary

Large population-based studies are needed to establish the magnitude and duration of the recently suggested association between arterial and venous thromboembolism. In 1997–98, all inhabitants of Groningen, the Netherlands, aged 28–75 years (n = 85 421), were invited to participate in a study that followed and monitored responding subjects (n = 40 856) for venous and arterial thromboembolism until 2009. Thromboembolism was verified with national registries of hospital discharge diagnoses and death certificates, anticoagulation clinic and medical records. During a median follow-up of 10·7 years, 549 participants developed venous thromboembolism and 3283 developed arterial thromboembolism. Annual incidence of arterial thromboembolism after venous thromboembolism was 2·03% [95% confidence interval (CI), 1·48–2·71], compared to 0·87% (95% CI, 0·84–0·90) in subjects without venous thromboembolism. The hazard ratio (HR) of arterial thromboembolism after venous thromboembolism was 1·40 (95% CI, 1·04–1·88) after adjustment for age, sex and cardiovascular risk factors. This risk was highest during the first year after venous thromboembolism [annual incidence, 3·00% (95% CI, 1·64–5·04); adjusted HR, 2·01 (95% CI, 1·19–3·40)] and after an unprovoked event [annual incidence, 2·53% (95% CI, 1·68–3·66); adjusted HR, 1·62 (95% CI, 1·11–2·34)]. This study showed that subjects with venous thromboembolism are at increased risk for arterial thromboembolism, particularly in the first year after venous thromboembolism and after an unprovoked event.

Keywords: arterial thromboembolism, venous thromboembolism.

The concept that arterial and venous thromboembolism are separate pathophysiological entities has been challenged (Lowe, 2006). Prandoni *et al* (2003) were the first to report a twofold increased risk for the presence of atherosclerotic plaques in patients with unprovoked deep vein thrombosis. Since then, several studies have examined the relationship between venous thromboembolism and the risk of subsequent arterial thromboembolism and confirmed a relationship between the two diseases. However, their generalizability is limited due to either a rather small sample-size (Becattini *et al*, 2005; Bova *et al*, 2006), a patient-based cohort (Becattini *et al*, 2005; Prandoni *et al*, 2006) or a lack of controls (Schulman *et al*, 2006). Also, some studies were limited by possible misclassification of outcome events due to the retrospective way in which the cardiovascular events were obtained (Spencer *et al*, 2008; Klok *et al*, 2009). In a recent meta-analysis (Becattini *et al*, 2010) no adjustments for age could be made. Age is a strong confounder to the risk of both venous and arterial thromboembolism, hence, based on this meta-analysis, we can not firmly conclude that the higher incidence of arterial thromboembolism after venous thromboembolism is truly related to previous venous thrombotic disease, as it can also merely be a result of ageing. The limitations of the abovementioned studies preclude an accurate estimation of the absolute incidences of cardiovascular arterial disease in patients with venous thromboembolism.

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This information, however, is important for the clinical management of these patients. A large population-based study was performed, in which the limitations discussed above were taken into account (Sorensen *et al*, 2007). This study found a two- to three-fold increased risk of arterial thromboembolism after first venous thromboembolism, predominantly in the first year following initial venous thromboembolism (Sorensen *et al*, 2007). However, large population-based studies on this issue are still needed to further establish the magnitude and duration of the association between arterial and venous thrombosis.

The Prevention of REnal and Vascular ENd stage Disease (PREVEND) Study (Hillege *et al*, 2001) offered us the opportunity to investigate the incidence of arterial and venous thrombotic disease in a large population-based cohort. We intended to use this study to advance our understanding of both arterial and venous thrombotic disease and provide further insight into the clinical course of patients with venous thromboembolism. Our aims were to establish whether venous thromboembolism is a risk factor for subsequent arterial thromboembolism, and to determine the absolute risk of arterial thromboembolism after venous thromboembolism, in a prospectively followed population-based cohort of more than 40 000 subjects.

Methods

Study population

This study was conducted on participants in the PREVEND Study, which was designed to prospectively investigate the natural course of albuminuria and its relationship with renal and cardiovascular disease in a large cohort drawn from the general population. Within the PREVEND Study design, arterial thromboembolic events were collected prospectively. Details of this study have been published previously (Hillege *et al*, 2001) and can be found at http://www.prevend.org. In 1997–98, all inhabitants of the city of Groningen, the Netherlands, aged 28–75 years (n = 85 421) were sent a postal questionnaire and a vial to collect an early morning urine sample. A total of 40 856 subjects (47·8%) responded. Their observation time started at study entry and ended at time of arterial thromboembolism, moving out of the city, death or end of study (January 2009).

All participants gave written informed consent. The PREVEND Study was approved by the local medical ethics committee and was conducted in accordance with the guidelines of the Declaration of Helsinki.

Definition of thrombotic events

To identify subjects with arterial and venous thromboembolism, the databases of the national registry of hospital discharge diagnoses (Prismant, Utrecht, the Netherlands) and death certificates (Central Bureau of Statistics, The Hague/Heerlen, the Netherlands) were linked yearly to the PREVEND database. In addition, the database of the regional anticoagulation clinic, which monitors the anticoagulant therapy of all inhabitants of the city of Groningen, was searched for venous events. When available, data on subjects with venous thromboembolism according to any of the abovementioned databases was confirmed by patients' medical records (n = 522). Arterial thromboembolism was predefined as acute myocardial infarction [International Classification of Diseases (ICD)-code 410], acute and subacute ischaemic heart disease (411), occlusion or stenosis of the precerebral (433) or cerebral arteries (434), coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA), and other vascular interventions, such as percutaneous transluminal angioplasty or bypass grafting of aorta and peripheral vessels (Oterdoom *et al*, 2009).

Deep vein thrombosis had to be confirmed by compression ultrasound, and pulmonary embolism by ventilation/perfusion lung scanning, spiral computed tomography, or at autopsy. When deep vein thrombosis and pulmonary embolism were diagnosed simultaneously, this was classified as pulmonary embolism. Only deep vein thrombosis and pulmonary embolism were considered in the present study, other types of venous thrombosis were not included. Venous thromboembolism was classified as being provoked when it had occurred at or within 3 months after exposure to an exogenous risk factor including surgery, trauma, immobilization for more than 7 d, pregnancy, puerperium, the use of oral contraceptives or hormonal replacement therapy, or malignancy. Venous thromboembolism was classified as unprovoked when no such exogenous risk factor was present.

Measurements

The questionnaire provided information about the presence of established risk factors for cardiovascular disease. Subjects were classified as being diabetic when they gave a positive answer when questioned if they had been diagnosed with diabetes by a physician, regardless of the type of anti-diabetic treatment. Subjects were considered hypertensive or dyslipidaemic when they positively answered the question regarding whether high blood pressure or high cholesterol, respectively, had ever been measured. Those who reported smoking or having smoked cigarettes during the previous 5 years were regarded as smokers. A history of myocardial infarction or stroke was considered present if subjects positively answered the question regarding whether they ever suffered from myocardial infarction or ischaemic stroke.

Morning urinary albumin concentration was established by a commercial immunoturbidimetry assay with sensitivity of 2·3 mg/l and inter- and intra-assay coefficients of variation of 2·2% and 2·6% respectively (BN II, Dade Behring Diagnostica, Marburg, Germany) (Hillege *et al*, 2001, 2002).

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First morning urine was used for analysis. Albuminuria was considered elevated at a concentration of 20 mg/l or more (Bangstad *et al*, 1991).

Statistical analysis

We estimated the absolute risk of arterial thromboembolism in subjects with and without venous thromboembolism to assess whether venous thromboembolism is a risk factor for arterial thromboembolism. The absolute risk was expressed as an annual incidence and was calculated by dividing the number of arterial events by the time at risk. The 95% confidence intervals (CIs) around the annual incidences were assessed with the Poisson distribution assumption. A time-varying exposure Cox proportional hazard model was used to estimate whether venous thromboembolism was a risk factor for arterial thromboembolism. With this model, we accounted for differences in the onset of venous thromboembolism, i.e. subjects were allocated to the non-venous thromboembolic group and added follow-up time to this group as long as they did not develop venous thromboembolism. At the time that subjects developed venous thromboembolism they switched to the venous thromboembolic group and started adding follow-up time to this group. Adjustments were made for age, sex, hypertension, dyslipidaemia, diabetes mellitus, smoking status, elevated albuminuria and history of arterial thromboembolism. Based on clinically relevant differences, preplanned sensitivity analyses were performed for the subgroups of venous thromboembolism (i.e. deep vein thrombosis *versus* pulmonary embolism and unprovoked *versus* provoked venous thromboembolism). Furthermore, *a priori* planned subanalyses were performed for the first year of follow-up after venous thromboembolism *versus* the rest of follow-up, to investigate the persistence of venous thromboembolism as a risk factor through time.

As hospitalization bias can cause misclassification of outcome events due to differences in monitoring subjects with or without venous thromboembolism, an additional sensitivity analysis was performed in which only the arterial thromboembolic outcome events myocardial infarction, ischaemic stroke or death due to arterial thromboembolism were regarded. Categorical data are presented as counts and percentages, continuous variables as medians with interquartile ranges (IQR). Statistical significance was considered as 2-tailed $P < 0{\cdot}05$. Statistical analyses were performed using PASW version 18·0 (IBM SPSS, Chicago, IL, USA) and SAS version 9·2 (SAS Institute, Inc, Cary, NC, USA).

Results

Study population

Baseline characteristics are shown in Table I. Out of 40 856 participants 46% was male. Median follow-up time was 10·7 (IQR, 8·8–11·0) years. Median age at enrolment was 60 (IQR, 48–68) and 48 (IQR, 39–60) years for subjects with and without venous thromboembolism respectively. Venous thromboembolism occurred in 549 subjects at a median age of 64 years (IQR, 53–73). In 256 subjects the venous event was secondary to an external risk factor, 249 events were unprovoked. In 44 events the presence or absence of an external risk factor could not be assessed from medical records. Arterial thromboembolism occurred in 3283 subjects (ICD-code 410, 33%; 411, 29%; 433, 5%; 434, 14%; CABG, 8%; PTCA, 5%; other, 6%). Forty-five subjects with venous thromboembolism subsequently developed arterial thromboembolism at a median age of 72 years (IQR, 65–78). In the group without venous thromboembolism, 3238 subjects developed arterial thromboembolism at a median age of 69 years (IQR, 60–74). The type of thromboembolic event is shown in Table II. Type of arterial thromboembolic event (ICD-9 coding) was equally distributed between the subjects with and without venous thromboembolism (data no shown).

Table I. Baseline characteristics.

	Subjects with venous thrombosis	Subjects without venous thrombosis
Total	549 (100)	40 307 (100)
Male	260 (47)	18 365 (46)
Age at enrolment, years	60 (48–68)	48 (39–60)
Cardiovascular risk factors		
Hypertension	197 (36)	11 642 (29)
Dyslipidaemia	83 (15)	5566 (14)
Diabetes mellitus	18 (3)	1033 (3)
Current smoker	202 (37)	16 946 (42)
Microalbuminuria ($\geq$ 20 mg/l)	60 (11)	3140 (8)
History of arterial thromboembolism	30 (6)	1749 (4)

Continuous variables are presented as median (IQR), categorical variables as number (%).

Table II. Type of thrombotic event

	Number (%)
Venous thromboembolisn	549 (100)
Deep vein thrombosis	313 (57)
Pulmonary embolism	175 (32)
Deep vein thrombosis and pulmonary embolism	61 (11)
Arterial thromboembolism	3283 (100)
Acute myocardial infarction	1079 (33)
Acute and subacute ischaemic heart disease	966 (29)
Occlusion or stenosis of the precerebral arteries	173 (5)
Occlusion or stenosis of the cerebral arteries	448 (14)
Coronary artery bypass grafting	258 (8)
Percutaneous transluminal coronary angioplasty	149 (5)
Other vascular interventions	210 (6)

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In the patients with venous thromboembolism, the median treatment time with anticoagulation was 6 (IQR, 3–10) months. Of the 45 subjects who developed arterial thromboembolism after venous thromboembolism, 17 subjects were still on anticoagulant therapy. One subject had stopped taking anticoagulant therapy <1 month before developing arterial thromboembolism, in all others the interval between cessation of anticoagulant and arterial thromboembolism was longer than 1 month.

In 9547 out of 40 856 participants, follow-up ended prematurely at time of non-arterial and non-venous vascular event (n = 220, 0·5%), non-cardiovascular death (n = 2222, 5·4%) or moving out of the city (n = 7105, 17·4%).

Risk of arterial thromboembolism after venous thromboembolism

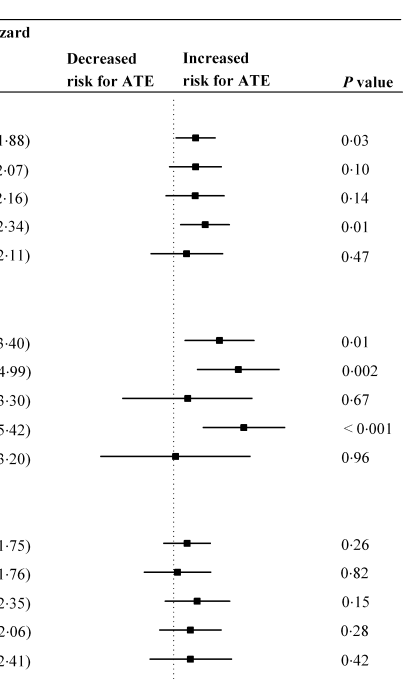
Figure 1 shows the risk of arterial thromboembolism after venous thromboembolism. The annual incidence of arterial thromboembolism after prior venous thromboembolism was 2·03% (95% CI, 1·48–2·71), compared to 0·87% (95% CI, 0·84–0·90) in subjects without venous thromboembolism. The crude hazard ratio (HR) of subsequent arterial thromboembolism was 2·24 (95% CI, 1·67–3·00, $P < 0·001$) in subjects with venous thromboembolism, compared to subjects without. After adjustment for age, sex, cardiovascular risk factors and previous arterial thromboembolism, the HR was 1·40 (95% CI, 1·04–1·88, $P = 0·03$). Within this model, age was a strong confounder as adjustment for age only resulted in a HR of 1·43 (95% CI, 1·06–1·92, $P = 0·02$).

Our preplanned subgroup analysis of venous thromboembolism indicated that the differences between subjects with deep vein thrombosis and subjects with pulmonary embolism were minimal. With an adjusted HR of 1·62 (95% CI, 1·11–2·34, $P = 0·01$), subjects with unprovoked venous thromboembolism were seemingly at higher risk of arterial thromboembolism than subjects with provoked venous thromboembolism [adjusted HR of 1·22 (95% CI, 0·71–2·11, $P = 0·47$)].

Risk of arterial thromboembolism was highest within the first year after venous thromboembolism with an annual incidence of 3·00% (95% CI, 1·64–5·04) and an adjusted HR of 2·01 (95% CI, 1·19–3·40, $P = 0·01$). This higher risk was predominantly found in subjects with deep vein or unprovoked thrombosis [adjusted HR, 2·68 (95% CI, 1·44–4·99, $P = 0·002$) and 2·91 (95% CI, 1·57–5·42, $P < 0·001$) respectively]. After 1 year of follow-up, the adjusted HR of arterial thromboembolism after venous thromboembolism decreased to 1·23 (95% CI, 0·86–1·75, $P = 0·26$).

To explore the influence of misclassification due to hospitalization bias, a subanalysis was performed in which cardiovascular outcome was limited to myocardial infarction,

	Observation years	No. ATE	Annual Incidence (%) (95% CI)	Crude Hazard Ratio* (95% CI)	Adjusted Hazard Ratio† (95% CI)	*P* value
Overall						
Venous thromboembolism (*n* = 549)	2222	45	2·03 (1·48—2·71)	2·24 (1·67—3·00)	1·40 (1·04—1·88)	0·03
Deep vein thrombosis (n = 313)	1378	25	1·81 (1·17—2·68)	1·99 (1·34—2·95)	1·40 (0·94—2·07)	0·10
Pulmonary embolism (n = 236)	844	20	2·37 (1·45—3·66)	2·59 (1·67—4·03)	1·39 (0·89—2·16)	0·14
Unprovoked VTE (n = 249)	1105	28	2·53 (1·68—3·66)	2·78 (1·92—4·04)	1·62 (1·11—2·34)	0·01
Provoked VTE (n = 256)	867	13	1·50 (0·80—2·56)	1·63 (0·95—2·82)	1·22 (0·71—2·11)	0·47
≤1 Year						
Venous thromboembolism	466	14	3·00 (1·64—5·04)	3·46 (2·04—5·84)	2·01 (1·19—3·40)	0·01
Deep vein thrombosis	271	10	3·69 (1·77—6·79)	4·24 (2·28—7·88)	2·68 (1·44—4·99)	0·002
Pulmonary embolism	195	4	2·05 (0·56—5·25)	2·34 (0·88—6·23)	1·24 (0·46—3·30)	0·67
Unprovoked VTE	221	10	4·52 (2·17—8·32)	5·17 (2·78—9·62)	2·91 (1·57—5·42)	< 0·001
Provoked VTE	203	3	1·48 (0·30—4·32)	1·68 (0·54—5·21)	1·03 (0·33—3·20)	0·96
>1 Year						
Venous thromboembolism	1756	31	1·77 (1·20—2·51)	1·92 (1·35—2·74)	1·23 (0·86—1·75)	0·26
Deep vein thrombosis	1107	15	1·36 (0·76—2·23)	1·47 (0·88—2·44)	1·06 (0·64—1·76)	0·82
Pulmonary embolism	649	16	2·47 (1·41—4·00)	2·67 (1·63—4·36)	1·43 (0·88—2·35)	0·15
Unprovoked VTE	884	18	2·04 (1·21—3·22)	2·22 (1·40—3·53)	1·29 (0·81—2·06)	0·28
Provoked VTE	664	10	1·51 (0·72—2·77)	1·62 (0·87—3·02)	1·29 (0·70—2·41)	0·42



VTE, venous thromboembolism; ATE, arterial thromboembolism
* Reference group are those without venous thromboembolism; in the overall analysis (n = 40 307) 3238 subjects developed ATE in 370 529 years of observation time
† Reference group are those without venous thromboembolism, adjusted for age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking status, elevated albuminuria and history of arterial thromboembolism
—■— Adjusted hazard ratio and 95% confidence interval

Fig 1. Risk of arterial thromboembolism after venous thromboembolism. 95% CI, 95% confidence interval.

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ischaemic stroke and cardiovascular death. Out of the 3283 subjects that developed an arterial event during follow-up, 1873 subjects developed myocardial infarction, ischaemic stroke or cardiovascular death. Twenty-seven of these arterial thromboembolic events developed subsequent to venous thromboembolism, while 1846 subjects did not suffer from prior venous thromboembolism. The annual incidence of myocardial infarction, ischaemic stroke or cardiovascular death in subjects with previous venous thromboembolism was 1·22% (95% CI, 0·81–1·77), compared to 0·49% (95% CI, 0·47–0·52) in subjects without previous venous thromboembolism. The overall crude HR of myocardial infarction, ischaemic stroke or cardiovascular death was 2·34 (95% CI, 1·60–3·42, $P < 0·001$) in subjects with venous thromboembolism, compared to subjects without. Multivariate analysis showed an overall adjusted HR of 1·42 (95% CI, 0·97–2·08, $P = 0·07$). Within the first year, this adjusted HR was 1·93 (95% CI, 0·96–3·87, $P = 0·06$). After 1 year of follow-up, the adjusted HR of myocardial infarction, ischaemic stroke or cardiovascular death after venous thromboembolism decreased to 1·28 (95% CI, 0·81–2·01, $P = 0·29$).

Discussion

This large population-based cohort study showed that subjects with previous venous thromboembolism are at increased risk to develop arterial thromboembolism. Although age was a strong confounder to this risk, the risk was still 1·4-fold increased after adjustment for age, sex, cardiovascular risk factors and history of arterial thromboembolism.

The overall absolute risk for arterial thromboembolism in subjects with venous thromboembolism was as high as 2·0% per year and even 3·0% during the first year after a diagnosis of venous thromboembolism. These values approach the absolute risk of recurrent venous thromboembolism (Heit *et al*, 2000; Christiansen *et al*, 2005). These data indicate that clinicians should be aware of the possibility of arterial thromboembolism, as well as recurrent venous thromboembolism. It also implicates that the treatment of patients with venous thromboembolism may have to be reconsidered. A meta-analysis concluded that acetyl salicylic acid, known for its preventive effect for cardiovascular disease, is also effective in preventing venous thrombosis (Karthikeyan *et al*, 2009). As yet, however, there is insufficient evidence to advise a combination of vitamin K antagonists and antiplatelet therapy in order to prevent both recurrence and arterial thromboembolism after a first venous thromboembolism. Two ongoing studies (Warfasa, agnellig@unipg.it and Aspire, aspire@ctc.usyd) address this issue. Another option might be to prescribe statins to patients with venous thromboembolism. In addition to their lipid-lowering and cardioprotective capacity, these drugs also appear to decrease the risk of venous thromboembolism (Agarwal *et al*, 2010).

Our results showed that the risk of arterial thromboembolism is highest during the first year after venous thromboembolism, especially in patients with an unprovoked event. This finding is in accordance with other studies (Sorensen *et al*, 2007; Klok *et al*, 2009). The early occurrence of cardiovascular events is difficult to understand, as patients with venous thromboembolism usually receive anticoagulant therapy in the first 3–6 months following their event and anticoagulant therapy is known to prevent cardiovascular events (Anand & Yusuf, 1999). In the early 1960s it was observed that an increased risk of cardiovascular events occurred after cessation of oral anticoagulant therapy (Dinon & Vander Veer, 1960). This high risk was assigned to a rebound effect on coagulant factors (Grip *et al*, 1991; Genewein *et al*, 1996; Ascani *et al*, 1999). This notion, however, was not corroborated by others (Van Cleve, 1965; Sharland, 1966; Tardy *et al*, 1997) and therefore remains controversial. In our cohort, only one subject developed arterial thromboembolism within a month after cessation of anticoagulant therapy, indicating that the presence of a rebound effect is unlikely.

Given these considerations, we hypothesize that the high risk of arterial thromboembolism within the first year after venous thromboembolism suggests that a joint mechanism relates the two diseases. The presence of underlying pathology affecting the venous system might also affect the arterial system. The high risk of arterial thromboembolism in subjects with an unprovoked venous event compared to those with a provoked event supports this idea, as does our finding that the relationship between arterial and venous thromboembolism persists after adjustment for self-reported cardiovascular risk factors. Which underlying pathology could relate the two diseases cannot be concluded from our study. An explanation could be bodyweight. Obesity is related to a higher risk of arterial (Hubert *et al*, 1983; Yusuf *et al*, 2004) and venous thromboembolism (Tsai *et al*, 2002; Stein *et al*, 2005). This might partly explain the relationship between arterial and venous thromboembolism through endothelial damage and/or the related changes in the levels of procoagulant proteins (Arcaro *et al*, 1999; Rosito *et al*, 2004). However, in a subset of patients for whom data on body mass index was available, adjustment for body mass index did not affect the risk of arterial thromboembolism after venous thromboembolism (data not shown).

Our study has both strengths and limitations. The strengths include the large population-based cohort, long follow-up time, prospectively collected data on arterial events, estimation of absolute risks and the adjustments made for age and sex in all analyses. A limitation of our study is that the data on cardiovascular risk factors were collected using self-reported histories at baseline. Data on the development of arterial cardiovascular risk factors during follow-up is not available. Furthermore, data regarding anticoagulant therapy were only available for the subjects who developed venous thromboembolism during follow-up. Hence, the use of anticoagulants was not included in our multivariate analyses and so we were not able to address the recent finding that antico-

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agulation therapy might accelerate arterial calcification (Rennenberg *et al*, 2010). The incidence of venous thromboembolism in our cohort may be underestimated as venous thromboembolism cases were retrospectively identified. Nonetheless, as compared with other prospective studies, our annual incidence of 0·15% is rather high as our cohort was confined to individuals younger then 75 years (Naess *et al*, 2007). Lastly, the higher risk of arterial thromboembolism after venous thromboembolism may be spurious due to misclassification of arterial thromboembolism caused by hospitalization bias. Nonetheless, our subanalysis with outcome restricted to myocardial infarction, ischaemic stroke and death due to arterial thrombosis, confirmed the primary analysis. Therefore, we conclude that misclassification was only marginal, if present. As shown in Fig 1, subgroup analyses were limited due to small numbers of arterial events, resulting in wider confidence intervals. For the same reason, we refrained from assessing differences in pulmonary embolism *versus* deep vein thrombosis and unprovoked *versus* provoked venous thromboembolism in this sensitivity analysis with restricted arterial outcome.

We conclude from this large cohort study that subjects with venous thromboembolism are at an increased risk to develop arterial thromboembolism. This risk is especially high in the first year after venous thromboembolism and after an unprovoked event. The risk persists after adjustment for age, sex, cardiovascular risk factors and previous arterial thromboembolism. Our findings implicate that the care for patients with venous thromboembolism should not only focus on the prevention of recurrent venous thromboembolism but also on the prevention of arterial thromboembolism.

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Author contributions

I.M. van Schouwenburg had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gansevoort, Lijfering, Veeger. Acquisition of data: Van Schouwenburg, Mahmoodi, Visser. Analysis and interpretation of data: Van Schouwenburg, Gansevoort, Mahmoodi, Kluin-Nelemans, Lijfering, Veeger. Drafting of the manuscript: Van Schouwenburg. Critical revision of the manuscript for important intellectual content: Van Schouwenburg, Gansevoort, Mahmoodi, Visser, Kluin-Nelemans, Lijfering, Veeger. Statistical analysis: Van Schouwenburg, Lijfering, Veeger. Obtained funding: Gansevoort. Administrative, technical, or material support: Van Schouwenburg, Gansevoort, Mahmoodi, Visser, Kluin-Nelemans, Lijfering, Veeger. Study supervision: Kluin-Nelemans, Lijfering, Veeger.

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Disclosure of conflict of interest

All authors report no conflicts of interest.

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